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Factors on development and severity of acute radiodermatitis: prospective single-center study

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ABSTRACT

Aim: Although prior literature has examined the treatment and patient-associated factors affecting the development and severity of acute radiodermatitis, there are relatively few prospective studies evaluating both. This study was prospectively designed to evaluate factors affecting the development and extent of radiation-induced acute skin toxicity called radiodermatitis (RD).

Material and Method: A total of 63 patients who underwent radiotherapy (RT) in Ankara Atatürk Research and Education Hospital between July 2017 and October 2018 were evaluated. Patients' demographic status, disease/treatment details, hemoglobin, ferritin, folic acid, Vit B12, and hemoglobin A1c values were recorded. The development and grade of RD were evaluated weekly by the same radiation oncologist using the Radiation Therapy Oncology Group (RTOG) radiation toxicity guideline.

Results: There was no significant relationship between the development of any degree of RD and gender, concomitant chemotherapy (CT), pre-RT CT, comorbid disease, RT technique and blood parameters (Hb, Hba1c, ferritin, folic acid and B12). The development of grade 2-3 RD was significantly affected by the number of operations (p=0.032) and total dose of RT (p=0.008). In patients with grade 2/3 RD, the RT dose at which RD first appeared was 20 Gy (range, 14-36); in patients with grade 1 RD, this value was 32 Gy (range, 16-56) (p=0.018).

Conclusion: There is no significant relationship between the development of acute radiodermatitis and Hba1c, hemoglobin, ferritin, B12 and folic acid levels. There was a significant correlation between grade of RD and repeated surgery, increase in total RT dose and early onset of RD.

Keywords: Radiotherapy, acute radiodermatitis, prospective

INTRODUCTION

Radiotherapy remains an essential component of cancer treatment, with nearly ½ of all cancer patients receiving RT during their illness (1). Radiodermatitis (RD) is skin toxicity of ionizing radiation, and approximately 95% of cancer patients receiving RT experience some form of RD, including erythema, dry and moist desquamation. These skin reactions often cause itching, and pain. However, RD is mostly moderate, with only 15-25% of it being severe (2,3). RD is often observed in patients receiving breast, head and neck, vulva, and sarcoma RT (2-4). The underlying causes are examined under two main headings: Treatment and patient-related factors (**Table 1**). As a result of RD, it causes a significant decrease in the quality of life of patients. In addition, the treatment of patients can be interrupted. This may lead to undesirable results in terms of oncological outcomes (5). Different parameters and indexes are being developed for the evaluation of RT (6,7). Also many treatment methods are being tried for the treatment of RD and there is no standard treatment. In the treatment of RD; hyperbaric oxygen therapy (HBOT), local antibiotics, herbal agents (aloe vera, calendula, etc), topical vitamins (ascorbic acid (ASC), pantothenic acid, etc), endogenous agents (hyaluronic acid (HA), epidermal growth factor (EGF) etc), pharmaceuticals (corticosteroids, statins etc) can be used (8). Oncological Nurse Forum (ONS) published a guideline in 2020 for the standardization of heterogeneous practices. This review does not recommend the use of aloe vera and curcumin which is frequently used according to this guideline, except in clinical studies. In addition, washing and skin care are recommended instead of topical nonsteroids. Topical steroids have been recommended in addition to skin washing in patients with itching and pain. However, even in most of the recommendations there is no

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consensus and the strength of the recommendation is weak (9). Finkelstein's published in 2022; Multinational Association for Supportive Care in Cancer (MASCC), British Columbia Cancer Agency (BCCA), Cancer Care Manitoba (CCMB), Oncology Nursing Society (ONS), Society and College of Radiographers (SCoR), and International Society of Nurses in Cancer Care (ISNCC) guidelines have been reviewed.All of these guidelines encourage the use of topical corticosteroids and recommended washing with soap and water. There is no consensus, especially regarding silver sulfadiazine, which is frequently prescribed by dermatologists.In this review, the necessity of further studies for RD was emphasized. If evaluated in the light of current literature, there is no single agent that is effective in RD (10).

Table 1. Factors affecting RD

Treatment-related parameters	Patient-related parameters
• Total dose	• Obesity
• Field Size	• Diabetes mellitus
• Fraction dose	• Malnutrition
• Energy	• Ethnic origin
• Use of bolus	• Age
• Number of beams	• Sex
• Type of chemotherapy	• Smoking
• Overall treatment time	• Genetic factors
	• Stage

RD: Radiodermatitis

The most basic approach is the evaluation and close follow-up of the patient in terms of prevention of RD. Pre-evaluation of risky groups is especially important in this respect. The presence of hematological parameters predicting RD is not clear. In previous studies, the relationship between these factors and RD has been investigated for different types of cancer (4,11). It is emphasized that some anemia parameters such as Ferritin, B12, and Folic acid should be evaluated about RD (4). In current study, the relationship between hematological parameters and the development of RD was investigated prospectively in a single center. There is limited literature data on the subject, and analysis will be made about whether there are hematological parameters predicting RD.

MATERIAL AND METHOD

All procedures performed in studies involving human participants were by the institutional and/or national research committee's ethical standards; and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Institutional Review Board approval was obtained for this study. The study was approved by the Ethics Committee of Ankara Yıldırım Beyazıt University Training and Research Hospital in July 2017 (Date: 12.07.2017, Decision No: 153).

Between July 2017-October 2018, 63 adult patients with stages 1-4, according to American Joint Committee on Cancer (AJCC) ver 8, treated with curative RT for head and neck, breast, vulva, sarcoma, and skin cancer in a tertiary radiation oncology clinic in Ankara were evaluated prospectively. Patient files and hospital electronic system data were used for data collection. The patients' demographic status, tumor size, disease stage, adjuvant treatment, weekly acute side effect assessment, and various treatments were noted.

Patients Selection

Patients who were in contact with the skin of the RT target area were included in the study. Patients with a pathological diagnosis and complete patient file data were prospectively evaluated in the study. Patients under the age of 18 without a pathological diagnosis were excluded. Patients with bone marrow involvement and chronic hematological disease were also excluded from the study.

Patients Simulation, Contouring and Planning

The planning CT of the patients was taken with the Aquilion LB Toshiba device at 3 mm cross-section and without contrast. Current contouring guides were used for contouring (12,13). Patients were treated with Helical Tomotherapy and Elekta Synergy Platform devices. The maximum dose in PTV was not exceeded by 110% in all plans.

Evaluated blood parameters

One week before the start of RT, complete blood count, ferritin, folic acid, B12, and hemoglobin A1c were requested from all patients.

Primary Endpoint

The primary endpoint is the evaluation of the formation and degree of acute RD. Skin changes in the RT field were examined by the same physician every week according to the Radiation Therapy Oncology Group (RTOG) manual to prevent inter-observer differences (**Table 2**) (14). The degree of RD is divided into 2 groups: grade 0-1 RD and grade 2-3 RD. Patients who were not followed up for acute side effects regularly were excluded from the study.

Table 2. RTOG acute radiation morbidity scoring criteria in skin (6)

Grade	Change
0	No change over baseline
1	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating
2	Tender or bright erythema, patchy moist desquamation/ moderate edema
3	Confluent, moist desquamation other than skin folds, pitting edema
4	Ulceration, hemorrhage, necrosis

RTOG: Radiation Therapy Oncology Group

Statistical Analysis

IBM SPSS Statistics v.20 (Armonk, NY: IBM Corp.) was used for statistical analysis. Non-parametric tests were used because the variables were distributed normally with visual and analytic methods. Mann-Whitney U test was used for the independent 2 groups. In the categorical two variables analysis, Chi-Square and Fisher -s Exact tests were used. The level of statistical significance was accepted at $p < 0.05$.

RESULTS

The patients' demographics are summarized in **Table 3**. The results of the anemia and diabetic profile values of the patients are presented in **Table 4**. RT technique (p=0.67), gender (p=0.27), concomitant chemotherapy (CT) (p=0.58), preRT CT (p=0.57), age (p=0.60), the presence of diabetes mellitus (DM) (p=0.50), Hb, HbA1c, ferritin, B12 and folic acid values were not significantly affecting the formation of RD.

Table 3. Patient demographics

Gender	
Male	25 (38.1%)
Female	38 (60.3%)
RT Technique	
IMRT	39 (61.9%)
3D RT	24 (38.1%)
Primer	
Head and Neck	22 (34%)
Breast	28 (44%)
Skin	6 (9.5%)
Sarcoma	4 (6.3%)
Vulva	3 (4.8%)
Stage	
1	7 (11%)
2	22 (34.9%)
3	25 (39.7%)
4	8 (12.7%)
DCIS	1 (1,6%)
Operation	
No	16 (25.4%)
Yes	47 (74,6%)
Concurrent CT	
Yes	35 (55,6%)
No	28 (44.4%)
CT before RT	
Yes	36 (57.1%)
No	27 (42.9%)
Comorbid Disease	
Yes	36 (57.1%)
No	27 (42.9%)
DM	
Yes	13 (20.6%)
No	50 (79.4%)
Smoking	
Smoker	50 (79.4%)
Non- smoker	27 (42.9%)
RD	
Yes	60 (95.4%)
No	3 (4.8%)
Grade of RD	
0	3 (4.8%)
1	34 (54%)
2	25 (39.7%)
3	1 (1.6%)

IMRT: Intensity Modulated Radiation Therapy, 3DRT: 3 Dimensional Radiotherapy, DCIS: Ductal Carcinoma In Situ, CT: Chemotherapy, RT: Radiotherapy, DM: Diabetes Mellitus, RD: Radiodermatitis

Table 4. Anemia and diabetic profile parameters

Parameters	Values (median)
Hemoglobin	12.4 (8.7-16.4)
Ferritin	104 (9.72-1269)
HbA1c (For DM +)	5.8 (5.46- 9.05)
B12	322 (159-1630)
Folic acid	7.2 (1.75-20)
Fasting blood glucose	83 (60-185)
Postprandial blood glucose	110 (105-276)

DM: Diabetes Mellitus

In the whole study population, 47 patients (74.6%) underwent surgery: 40 (85.1%) of them had 1, and 7 (14.9%) of them had 2 or more operations. Grade 2/3 RD was observed in 14 (35%) of the patients with 1 operation and 6 (85.7%) of the patients with more than 1 (p=0.032). A significantly higher rate of grade 2/3 RD was observed in patients with 2 or more operations (p=0.032).

No significant effect of RT fraction dose (1.8Gy vs. 2 Gy vs. 2.67 Gy) on RD was observed. A significant relationship was observed between RT total radiation dose and grade 2/3 RD (p=0.008) (**Figure 1**). The median total radiation dose was 50 Gy (range, 39-70) in patients with Grade 0/1 RD and 60 Gy in patients with grade 2/3 RD (range, 50-70 Gy) (p=0.008). The probability of grade 2/3 RD increased significantly with increasing total doses.

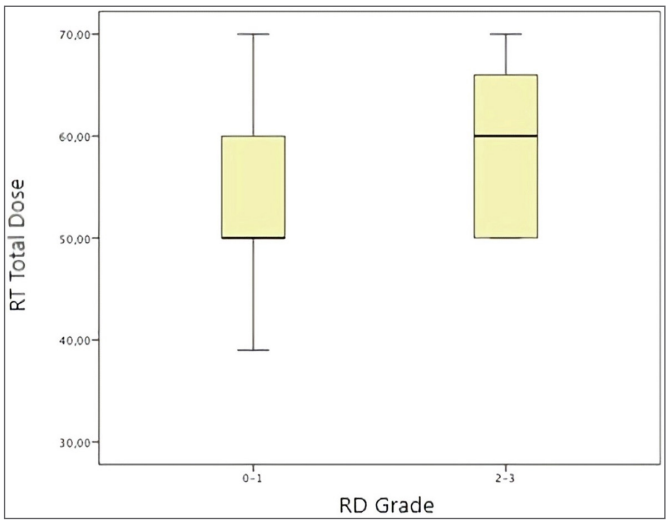

Figure 1. The risk of RD increases as the total dose of RT increases

In patients with grade 2/3 RD, the RT dose at which RD first appeared was 20 Gy (range, 14-36); in patients with grade 1 RD, this value was 32 Gy (range, 16-56) (p=0.018) (**Figure 2**). If grade 1 radiodermatitis started below 20 Gy, the risk of developing grade 2 and 3 RD increased. As the starting dose of grade 1 RD decreased, the risk of grade 2-3 RD increased throughout the treatment period.

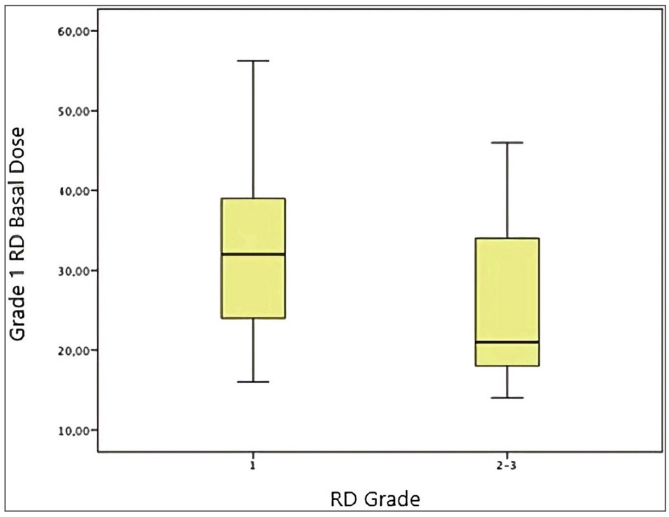

Figure 2. Relationship between the grade of RD and initial RT dose

DISCUSSION

In our study, no significant effect was found between RD development and blood levels of anemia and diabetic profile parameters. However, grade 2/3 RD is significantly affected by the number of operations performed by the patient before RT (p=0.032). A significantly higher rate of grade 2/3 RD was observed in patients with an operation number of 2 or more. A significant relationship was also observed between total radiation dose and grade 2/3 RD (p=0.008) (**Figure 1**). The median total dose was 50 Gy (range, 39-70) in patients with grade 0/1 RD; and 60 Gy (range, 50-70) in patients with grade 2/3 RD (p=0.008). In addition, patients with grade 2/3 RD had a median initial dose of 20 Gy (range, 14-36); In patients with grade 1 RD, the initial generation dose of RD was 32 Gy (range, 16-56) (p=0.018). The lower the threshold dose of RD, the higher the risk of grade 2/3 RD.

Radiation exposure to the skin causes cellular damage, aggravated by ROS formation and nucleic acid damage, and migration of inflammatory cells in the skin, and eventually, RD develops (15). Cellular damage is mainly observed in epidermal cells, basal epidermal cells, Langerhans cells, and endothelial and vascular cells (16). Increased cellular damage leads to an induced inflammatory cytokine and chemokine cascade. Chemokines and cytokines such as IL-1, IL-6, TNF-alpha, TGF-Beta, and histamine-like mediators increase in the micro-environment (17). In response to increased chemokines and cytokines, the endothelium is activated, and the expression of the adhesion molecules is accelerated and causes the migration of immune cells to the region, particularly leukocytes (17). Inflammation caused by the migration of immune cells increases the damage. In addition to these, stem cell loss due to RT negatively affects the skin's repair cycle (18). Histamine-like factors have shown increased capillary permeability and vasodilation. With increasing RT fractions, cellular damage increases, and if there is not enough time for repair, the damage becomes more evident towards the last stages of treatment (18,19). Dry desquamation develops due to erythrocytes' extravasation, and dry desquamation is usually the first clinical manifestation of RD. When RT damage is present in the basal cells and glandular tissue, epididymal necrosis with fibrinous exudate may occur. This is called moist desquamation. Finally, necrosis and ulceration of deeper tissues can be observed (17,20).

There was a relationship between total dose and RD by the literature. RT dose and fraction scheme play an important role in the development of RD (21). Consistent with the literature, a significant relationship was found between the total dose and RD in our study. In addition, a clinical RD initiation dose was noted in our study. Although dermal toxicity starts earlier in sensitive skin, it usually develops within 2-3 weeks (22,23). Dry desquamation starts in 3 weeks, nearly 30 Gy; moist desquamation starts in 4-5 weeks, nearly 45-50 Gy (4). Similar to our study, the time of first appearance of RD was also evaluated in Bontempo's prospective study, published in 2021 and including breast, head, neck and pelvic irradiation. According to this study, the first appearance of RD was approximately 11 days (24). In current study, in patients with grade 1 RD and not progressing to grade 2 or 3; the starting dose of grade 1 RD is 32 Gy (range, 16-56). In patients with grade 2-3 RD, the median dose at which RD occurs is 20 Gy (range, 14-36) (p=0.018). According to our study, it continued to be more severe in early-onset RD cases. Therefore, along with the RD grade, the dose at which grade 1 RD begins to occur should also be noted.

The low hemoglobin level can increase the radiosensitivity of the skin due to impaired tissue oxygenation. A limited number of studies evaluate the relationship between hemoglobin and RD (25,26). Gangopadhyay et al. (25) investigated the association between hemoglobin and mucocutaneous side effects in 227 patients with cervical cancer. In the patients receiving concurrent CT, patients with hemoglobin values of 12 or higher had a higher mucocutaneous side effect (p=0.001). On the other hand, in the study of Henke et al. (26), in 60 patients with head neck disease, lower hemoglobin levels were found to decrease the risk of RD, but the difference was not statistically significant (p=0.08). However, in our prospective study, no significant relationship was found between hemoglobin/ ferritin levels and RD.

The relationship between B12, folic acid levels and RT side effects is also a current research topic. These vitamins are important factors in DNA metabolism and wound healing (27). It is possible that there is a relationship between acute and chronic tissue damage due to radiation and vitamin values. In Debowska's research,

creams containing folacin were shown to improve skin conditions in patients receiving an RT (28). Our study did not demonstrate any relationship between blood folic acid and vitamin B12 levels and the timing and severity of RD. However, it would be more accurate to evaluate the difference in larger patient series with more homogeneous groups.

Smoking is known to impair wound healing by cutaneous vasoconstriction. Similarly, it may be thought that it adversely affects RD development with a similar mechanism (11,17). However, in the Kraus-Tiefenbacher study, no significant relationship was found between acute skin toxicities (erythema G0 versus G1 versus G2) and smoking during radiation therapy (p=0.064) in breast cancer (29). In the review published by Wong et al. in 2020, the effect of smoking on RT results and side effects in breast cancer patients was investigated (30). Skin changes were also analyzed in this review, and similar to our study, no article mentioned an increased risk in smokers. In this study, there was no significant relationship in terms of RD in smokers and nonsmokers patients.

RD development can be observed more frequently in elderly patients. because older age disrupts skin turnover (5,11,31,32). Advanced age is an unfavorable risk factor for many diseases (35). In general, although there is concern about an increase in side effects related to elderly patients, there is no significant increase in skin side effects (33). In the study of Wong et al. in 2021, it was observed that Older age was associated with increased risk of skin toxicities in 21 patients who underwent intraoperative radiotherapy (IORT) (34). However, unlike Wong's current study, many studies have not found a direct relationship between age and skin toxicity. Avoiding standard doses and fractions due to toxicity concerns in elderly patients has not been found to be correct in many recent publications (33,35). Similarly, no significant relation was found between RD development and RD grade and age in current study.

DM is a risk factor for RD when it causes adverse effects such as macrophage dysfunction, prolonged inflammatory phases, susceptibility to infection, and wound healing disorder (4,31). It was shown in the SBRT study of Kalman et al. that there was an increase in RT complications in patients with DM diagnosis (36). It is supported by studies that DM is a risk factor especially for radiation pneumonia (37). Similarly, in the study of Kuo et al., DM diagnosis was found to be significantly more risky in terms of infection and hematotoxicity, loss of body weight, and higher treatment-related mortality in head and neck patients (38). In our study, plasma blood glucose and Hba1c (for DM patients) values were evaluated, but no significant relationship could be detected.

Limitations of our study are small cohorts, not randomized and a single center study. RT areas and treatment doses are not homogeneous. However, the strength of the study is that it is prospective and all patients are evaluated by the same clinician. Randomized evaluation of patient groups with more similar treatments to detect factors predicting the development of RD will contribute more.

CONCLUSION

The severity of RD was associated with recurrent surgical intervention, RT total dose, and early onset of RD.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Yıldırım Beyazıt University Medical Faculty Clinical Researches Ethics Committee (Date: 12.07.2017, Decision No: 153).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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